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PATENT
Atty. Dkt. No.: 46403-1009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YAJUN GUO	)	Group Art Unit:	1644
	)		
	)	Examiner:	Dibrino, M.
Serial No.: 09/216,062	)		
	)		
Filed: December 18, 1998	)		
	)		
For: CELLULAR VACCINES AND IMMUNOTHERAPEUTICS AND METHODS FOR THEIR PREPARATION	)		

San Diego, California 92101
April 3, 2001

Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL RESPONSE

Dear Sir:

Further to the response file March 13, 2001, please enter the following amendments and consider the following remarks.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, with sufficient postage and an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date of Deposit: April ___, 2001

Signature: _____
Karen M. Cruz

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AMENDMENTS

Please cancel claims ____ with ut prejudice and new claims ____as follows:

--45. A method of preparing a pharmaceutical composition or therapeutic vaccine, said method comprising the steps of:

(a) providing a plurality of hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells;

(b) treating said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells to increase the levels of CD28, 4-1BB, or CTLA-4 molecules in said cells;

(c) providing a plurality of a bispecific monoclonal antibodies comprising one or more binding sites for one or more CD28, 4-1BB or CTLA-4 molecules on the surface of T cells in a patient mammal and one or more binding sites for gp55, gp95, gp115 or gp210 antigens;

(d) attaching said bispecific monoclonal antibodies to said cells; and

(e) thereafter collecting a pharmaceutically effective amount of said cells with said bispecific monoclonal antibodies attached thereto; wherein said steps (c) and (d) are performed either before or after said step (b).

46. The method of claim 45, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more hepatocellular carcinoma cells.

47. The method of claim 45, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more lymphoma cells.

48. The method of claim 45, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more colon carcinoma cells.

49. The method of claim 45, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more gastric cancer cells.

50. The method of claim 45, wherein said one or more CD28, 4-1BB or CTLA-4 molecules comprise one or more CD28 molecules.

51. The method of claim 45, wherein said one or more CD28, 4-1BB or CTLA-4 molecule comprise one or more 4-1BB molecules.

52. The method of claim 45, wherein said one or more CD28, 4-1BB or CTLA-4 molecule comprise one or more CTLA-4 molecules.

53. The method of claim 45, wherein said patient mammal is a human.

54. The method of claim 45, wherein the one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with IFN-γ.

55. The method of claim 45, wherein the one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with TNF-α.

56. The method of claim 45, wherein the one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with IFN-γ and TNF-α.

57. The method of claim 45, wherein said T cells are CD3+CD8+CD25+ T cells.

58. The method of claim 45, wherein said antibodies comprise two or more antigen binding sites for one or more gp55, gp95, gp115, or gp210 antigens on the surface of said one or

more hepatocellular carcinoma cells, lymphoma cells colon carcinoma cells or gastric cancer cells.

59. The method of claim 45, wherein said antibodies comprise two or more binding sites for said one or more CD28, 4-1BB or CTLA-4 molecules on the surface of T cells in said patient mammal.

60. The method of claim 45, wherein said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with 10-100 U of IFN-γ and 10-100 U of TNF-α.

61. The method of claim 45, wherein said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with 100 U of IFN-γ and 50 U of TNF-α.

62. The method of claim 46, where said hepatocellular carcinoma cells are hepa 1-6 cells.

63. The method of claim 47, wherein said lymphoma cells are EL-4 cells.

64. The method of claim 48, wherein said colon carcinoma cells are SMCC-1 cells.

65. The method of claim 45, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp55 antigens.

66. The method of claim 45, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp95 antigens.

67. The method of claim 45, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp115 antigens.

68. The method of claim 45, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp210 antigens.

69. The method of claim 45, wherein said collecting in step (e) comprises the step of removing said bispecific monocl nal antibodies not attached to said cells.

70. An immunogenic composition, comprising:

a pharmaceutically effective amount of one or more isolated autologous hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells which express one or more CD28, 4-1BB, or CTLA-4 molecules at a level higher than in said cells in a patient mammal; and

a pharmaceutically effective amount of one or more bispecific monoclonal antibodies comprising one or more binding sites for one or more CD28, 4-1BB or CTLA-4 molecules on the surface of T cells in a patient mammal, and one or more binding sites for said gp55, gp95, gp115, or gp210 antigens, wherein said bispecific monoclonal antibodies are attached to said cells, and wherein said composition is substantially free of bispecific monoclonal antibodies not attached to said cells.

71. The composition of claim 70, wherein said composition is isolated.

72. The composition of claim 70, wherein said composition is enriched. 112 2nd

73. The composition of claim 70, wherein said composition is purified.

74. The composition of claim 70, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more hepatocellular carcinoma cells.

75. The composition of claim 70, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more lymphoma cells.

76. The composition of claim 70, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more colon carcinoma cells.

77. The composition of claim 70, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells comprise one or more gastric cancer cells.

78. The composition of claim 70, wherein said one or more CD28, 4-1BB or CTLA-4 molecules comprise one or more CD28 molecules.

79. The composition of claim 70, wherein said one or more CD28, 4-1BB or CTLA-4 molecule comprise one or more 4-1BB molecules.

80. The composition of claim 70, wherein said one or more CD28, 4-1BB or CTLA-4 molecule comprise one or more CTLA-4 molecules.

81. The composition of claim 70, wherein said patient mammal is a human.

82. The composition of claim 70, wherein the one or more hepatocellular carcinoma, lymphoma, colon carcinoma cells or gastric cancer cells are treated with IFN-γ.

83. The composition of claim 70, wherein the one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with TNF-α.

84. The composition of claim 70, wherein the one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells are treated with IFN-γ and TNF-α.

85. The composition of claim 70, wherein said T cells are CD3+CD8+CD25+ T cells.

86. The composition of claim 70, further comprising a pharmaceutically acceptable carrier or excipient.

87. The composition of claim 70, wherein said antibodies comprise two or more antigen binding sites for one or more gp55, gp95, gp115, or gp210 antigens on the surface of said one or more hepatocellular carcinoma cells, colon carcinoma cells or gastric cancer cells.

88. The composition of claim 70, wherein said antibodies comprise two or more binding sites for said one or more CD28, 4-1BB or CTLA-4 molecules on the surface of T cells in said patient mammal.

89. The composition of claim 70, wherein said composition comprises two or more antibodies comprising one or more antigen binding sites for one or more gp55, gp95, gp115, or gp210 antigens on the surface of said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

90. The composition of claim 70, wherein said composition comprises two or more antibodies each comprising a binding site for a different one of said CD28, 4-1BB or CTLA-4 molecules.

91. The composition of claim 70, wherein said composition comprises two or more antibodies each attached to a different antigen.

92. The composition of claim 70, further comprising a pharmaceutically effective amount of IFN-γ, TNF-α, or both.

93. The composition of claim 70, wherein said hepatocellular carcinoma cells, lymphoma, colon carcinoma cells or gastric cancer cells are treated with 10-100 U of IFN-γ and 10-100 U of TNF-α.

94. The composition of claim 70, wherein said hepatocellular carcinoma cells, lymphoma, colon carcinoma cells or gastric cancer cells are treated with 100 U of IFN-γ and 50 U of TNF-α.

95. The composition of claim 74, where said hepatocellular carcinoma cells are hepa 1-6 cells.

96. The composition of claim 75, wherein said lymphoma cells are EL-4 cells.

97. The composition of claim 76, wherein said colon carcinoma cells are SMCC-1 cells.

98. The composition of claim 70, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp55 antigens.

99. The composition of claim 70, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp95 antigens.

100. The composition of claim 70, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp115 antigens.

101. The composition of claim 70, wherein said one or more gp55, gp95, gp115, or gp210 antigens comprise gp210 antigens.

102. The composition of claim 70, wherein said one or more hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells express said one or more CD28, 4-1BB or CTLA-4 molecules at a level 50% higher than the amount that said one or more CD28, 4-1BB or CTLA-4 molecules are expressed from hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells in a patient mammal.

103. The composition of claim 70, wherein said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells expresses said one or more CD28, 4-1BB or CTLA-4 molecules at a level 2 fold higher than the amount that said one or more CD28, 4-1BB or CTLA-4 molecules are expressed hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells in a patient mammal.

104. The composition of claim 70, wherein said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells expresses said one or more CD28, 4-1BB or CTLA-4 molecules at a level 10 fold higher than the amount that said one or more CD28, 4-1BB or CTLA-4 molecules are expressed from hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells in a patient mammal.

105. The composition of claim 70, wherein substantially all of said antibodies are attached to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

106. The composition of claim 70, wherein over 80% of said antibodies are attached to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

107. The composition of claim 70, wherein over 90% of said antibodies are attached to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

108. The composition of claim 70, wherein over 95% of said antibodies are attached to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

109. The composition of claim 70, wherein the composition is substantially free of said antibodies that are not bound to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.

110. The composition of claim 70, wherein a pharmaceutically effective amount of said antibodies are bound to said hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells.--.